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THE AMERICAN
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VOL. 105 DECEMBER, 1933 NO. 12

EDITORIAL

TEXTS FROM A CHEMISTRY LECTURE

PHILLIPS BROOKS, the famous hymnologist and cleric, used to say that a preacher's Sunday job was always easy, for he had all the length and breadth of an abundant Bible, wherefrom to choose his text—and then having chosen such, he could, by his preacher's prerogative, elect to talk on any subject other than his text.

Of course one does not have to be a preacher to achieve to such a privilege. Nor does one have to believe that the Bible is the only wealthy source of such material.

Only the other evening we listened to a well-delivered lecture on a certain phase of physical chemistry—when in spite of the excellence of the presentation—we went wool-gathering—except that we found many a text but nary a textile.

"Clear when viewed by transmitted light, cloudy with reflected light". So said the lecturer of a colloid mixture upon the counter. How untrue, thought we, when applied to the present state of things. After the last few hectic years, with all our schemes and themes gone awry, how, with hope and optimism transmitting their rays to and through the days ahead, we only *think* we see a clearer, cleaner road around the corner. For actually, how cloudy, how dark and uncertain is every tomorrow."

> "White are the hills ahead
> White, white with Dawn
> When reached at dusk—grey, grey, forlorn!"

and, "cloudy with reflected light".

Again how untrue—for it is from our reflections of the road behind that we must clearly gain our plan, and find our courage, for the unknown, untold road ahead. Our yesterdays *do* follow us—they constitute our lives and give meaning to our present deeds.

Then, much to the delight of certain young people in the audience, one of the professor's experiments refused to carry on, and proved an utter failure, in extenuation of which the speaker resorted to that

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trite and time-honored remark—"The experiment was not a success—but the principle remains the same."

And what a sermon might be woven around this exquisite text. How, if the principle be sound, and yet the experiment fails, either the experimenter or the raw materials of the reaction have been wrong. How importantly it brings to us the message that assurance of the success of any experiment large or small, with the animate or inanimate, with ourselves or with others, lies firstly in finding the correct principles—the fundamentals—and then insisting upon a soundness in the materials of the reaction and a guided plan of action by the experimenter himself.

Then, all other things being equal, the experiment must be a success—and listening, watching youth will find a will to learn and not a wish to laugh.

Then, too, the lecturer referred to another experiment in these words—"This is a time reaction and you may not see, before the end of the lecture, just what I should like you to see."

We did not!

But again—what a text.

How all of man's debts to the past and his obligations to posterity are involved in a similar picture. How the worthwhile seed he sows today will find another at the harvest, with the sower, deaf and dumb and dead.

"A Time reaction"—said the lecturer.

Said Byron,—

"Time! the corrector where our judgments err;
The test of truth and love;
The sole philosopher, for all beside are sophists."

Long before him, Euripedes said,—

"Time will discover everything to posterity,
It is a babbler, and speaks even when no question is put."

And it might have been the time of year—a wringing out of the old—a ringing in of the new, that moved us to such reflections.

In any event, we now venture the hope that when we next assume the role of lecturer, there will be some who, failing to find us intriguing in talk, will find in our unwitting words, or will frame from our feeble phrases, texts that may move them to think of sermons that *will* urge them to live their lives fuller and freer than ever before.

IVOR GRIFFITH.

ORIGINAL ARTICLES

ACHILLEA MILLEFOLIUM, Linné
CONSTITUENTS OF THE PETROLEUM ETHER EXTRACT OF OF THE BLOSSOMS

By R. L. McMurray*

Introduction

THE volatile oil of *Achillea Millefolium* Linné has been investigated over a period of 214 years by the various workers. But a search of the literature shows no systematic investigation of the non-volatile fatty portion of the plant. Therefore, an investigation of the non-volatile fatty oil of the plant was begun, to add to the phytochemical knowledge of this plant.

Experimental

The 1929 crop of *Achillea Millefolium* L. harvested from the Pharmaceutical Garden of the Wisconsin Pharmaceutical Experiment Station was air dried and then separated by hand into the flower heads and the remainder of the plant. The dried flower heads were ground to a No. 20 powder. More than 100 pounds of ground material were obtained.

An analysis of the 1928 crop, obtained from the same source, showed blossoms 48.03 per cent., leaves 12.66 per cent. and stems 39.30 per cent., all air dried and measured on a total of 57.25 pounds.

The work on the volatile oil, ash analysis, Dragendorff extractions, moisture and crude fiber determinations and historical review will be omitted in this article.

Extraction With Petroleum Ether

The material was extracted in the Lloyd extractor in capacity batches of fifteen pounds until a total of 100 pounds had been extracted, using refined petroleum ether as solvent. The extracts were combined and the petroleum ether removed by heating at about 70 degrees C. during exposure to a current of air produced by an electric fan. The resulting extract weighed 916 grams, and was a very dark green colored solid, of a fatty nature.

*School of Pharmacy, State College of Washington, Pullman.

Separation of the Volatile and Fixed Oils

The 916 grams of petroleum extract were steam distilled and the distillate cohobated. The volatile oil amounted to 36.8 cc., or 33 grams, representing 0.073 per cent. of the 100 pounds of air dried blossoms. The non-volatile oil retained in the distillation flask was collected and dried. It weighed 846 grams and represented 1.86 per cent. of the blossoms.

Fixed Oil

The crude fixed oil was of a dark green color, wax-like and solid at room temperature. The acid values were 36.4, 39.4 and 34.9, or an average value of 36.9; saponification values were 110.6, 114.1 and 109.7, or an average value of 111.5; iodine values of 56, 60 and 54, or an average value of 56.6. Much difficulty was experienced by interference of the green color. Attempts to remove the color were unsuccessful.

Saponification of the Fixed Oil

An 800 gram portion of the fixed oil was warmed on a steam bath until liquid and then stirred into a boiling solution of 89 grams of KOH (absolute) in 1 liter of 95 per cent. alcohol. The mixture was refluxed twelve hours. The alcohol was then recovered from the reaction mixture, leaving a soapy solution.

Extraction of the Unsaponifiable Material

The soapy liquid obtained after the removal of the alcohol from the saponification mixture was diluted with water and repeatedly extracted with ether by aid of a separatory funnel. The successive ether extracts were separated from aqueous soapy portion, combined together and then washed with water to remove the soapy material. The ether extracts were then dried over anhydrous sodium sulphate and filtered. The ether was then recovered, leaving a residue of nonsaponifiable material which amounted to 182 grams, or 22.75 per cent. of the original 800 grams of fatty material.

Insoluble Material

A portion of the saponification mixture was insoluble in water and in ether, and remained suspended between the ether and aqueous layers. This insoluble material was mechanically removed and dried. It amounted to 60 grams, or 7.5 per cent. of the original 800 grams of fatty material.

Examination of the Saponified Portion of the Fixed Oil

After the removal of the non-saponified material and the insoluble suspended portion, the aqueous solution containing the potassium salts of the fatty acids and other water soluble compounds (glycerol)

amounted to about 30 liters. This was concentrated on a steam bath by stirring continuously while exposed to a current of air, until it amounted to about six liters. The fatty acids were set free by adding about half a liter of sulfuric acid, diluted with water in the ratio of 1 to 4, while the liquid was vigorously stirred. The fatty acids separated as a black, tarry odoriferous mass. Resort was had to ether to recover these acids. Between the ether and aqueous layers a dark, insoluble suspended material was again in evidence. This was mechanically separated and amounted to 42 grams, or 5.25 per cent. of the original 800 grams of fatty material. The liberated fatty acids emitted the odors of the lower members of the fatty acid series, especially iso-valeric acid. The fatty acids amounted to 418 grams, or 52.5 per cent. of the original 800 grams of fatty material.

Separation of the Fatty Acids by the Lead-Ether Method

The saturated and the unsaturated fatty acids were separated by the method of Varrentrap and Gusserow. (1) More or less difficulty was encountered with this method, with the result that some material was lost. There was finally obtained 62 grams of unsaturated fatty acids, or 7.75 per cent., and 121 grams of saturated fatty acids, or 15.12 per cent. of the original 800 grams of fatty material. These combined amounted to 22.87 per cent., or a loss of 29.63 per cent. of the original fatty material by this method of separation of the two groups of acids.

The Unsaturated Fatty Acids

The lead salts of the unsaturated fatty acids were treated with 1:1 hydrochloric acid (1 part of 40 per cent. hydrochloric acid to 1 part of water) under ether, and yielded 62 grams of these acids, or 7.75 per cent. of the original 800 grams of fatty acids.

Sixty grams of the unsaturated fatty acids were treated with bromine according to the method of Lewkowitsch (2) by dissolving in two and a half liters of ether containing 5 per cent. glacial acetic acid, the solution cooled to 5 degrees C., and bromine added from a burette until a distinct bromine color was noticeable. In this way the bromine addition products were formed. The ethereal solution was allowed to stand five hours in an ice bath, but no precipitate occurred—nor on repetition. This indicated the absence of linolenic acid from this material.

Linoleic Acid

The ethereal solution was then washed with a saturated aqueous solution of sodium thiosulfate to remove excess bromine, and the ether recovered by distillation. The residue was then refluxed with petroleum ether, cooled, and the solution placed in the ice box (33-36 degrees F.) (1-3 degrees C.) for five hours. The precipitate thrown down in the cold was filtered off, the filtrate reduced to half of its initial volume, and again placed in the ice box for five hours. The second precipitate was removed. This was repeated until no more precipitate was obtained. The precipitates were then combined and amounted to six grams of linolic (acid) tetrabromide. After repeated recrystallizations from petroleum ether a melting point of 112 degrees C. was obtained. This was characterized as linolic (acid) tetrabromide. (3)

Oleic Acid

The petroleum ether was then recovered from the filtrates and the residue evaporated to dryness. This residue amounted to 40 grams. The bromine content was determined by the Stepanow (4) method and found to be 33.66 per cent., 33.03 per cent. and 33.56 per cent., or an average value of 33.4 per cent. Lewkowitsch (5) states that oleic (acid) dibromide contains 36.18 per cent. bromine. About two grams of the oleic dibromide were reduced with zinc and hydrochloric acid, the regenerated oleic acid recovered by the aid of ether, dissolved in 5 cc. of sulfuric acid (conc.) and tested with 1 cc. of a 1 per cent. alcoholic solution of vanillin superimposed upon the sulfuric acid layer (6). The characteristic violet coloration of oleic acid (compared by testing with known oleic acid) was obtained. This compound was characterized as being oleic (acid) dibromide.

Glycerol

The aqueous portion of the saponification mixture, after the removal of the fatty acids, was neutralized with sodium carbonate and concentrated on a steam bath. The sodium sulfate and sodium carbonate crystals were filtered off and the filtrate treated with siliceous earth and animal charcoal until practically colorless. This aqueous residue was then extracted with a solvent of 3 parts of alcohol (95 per cent.) and 1 part of ether, and the resulting extract concentrated on the steam bath. Only a small amount of extract was obtained. It is noted here, as an observation on the material for this investigation, that the material remaining after the steam distillation of the petroleum ether extract was hard and waxy in character. It really resembled carnauba wax

except for its color. Glycerol was tested for according to the methods given by Rosenthaler (7) and Kamm (8). The sodium hydroxide and copper sulfate test reacted positive; Fehling's solution positive; Schiff's reagent positive; ammoniacal silver nitrate test produced only a poor mirror. These tests indicated the presence of glycerol, but in relatively small quantities.

The Saturated Fatty Acids

The lead salts of the saturated fatty acids were treated with 1:1 hydrochloric acid, under ether, and yielded 121 grams of these acids, or 15.12 per cent. of the original 800 grams of fatty material.

The methyl esters of the saturated fatty acids were prepared by dissolving the acids in 250 cc. of methyl alcohol and 600 cc. of ether, adding 3 per cent. of 38 per cent. hydrochloric acid, 2 grams of granulated zinc and refluxing during sixteen hours. During this time a current of HCl gas was drawn through the reaction mixture.

The reaction mixture was cooled, and barium carbonate added to neutralize the free HCl and then this mixture was warmed during thirty minutes. The mixture was then repeatedly washed with a saturated solution of sodium chloride to remove the excess methyl alcohol. Six hundred cc. of ether were added to extract the methyl esters, the ether solution was separated, dehydrated with calcium chloride, filtered, and the ether recovered from the filtrate. The methyl esters weighed 100 grams.

The methyl esters were then transferred to a Claisson distilling flask. The flask was carefully insulated with asbestos, connected with an air condenser, leading into a fractional distillation receiver to obtain portions at different distilling temperatures, and the apparatus protected from drafts. The methyl esters were then fractionally distilled under reduced pressure.

Sample No.	Weight	Bath Temperature	Distillation Temperature	Pressure
1	4.3	155-210°	83-150°	3 mm.
1a	32.8	210-260°	150-176°	3 mm.
2	20.3	260-298°	176-200°	3 mm.
3	6.0	305-313°	185-222°	4 mm.
4	10.6 grams	338-342°	215-223°	4 mm.

It was more difficult to maintain low pressure and an even high temperature during the final stages of the distillation, due to breakdown of the joints of the apparatus and bumping of the esters by the intense heat.

Myristic Acid

Distillate No. 1, of the distilled methyl esters of the saturated fatty acids, amounted to 4.3 grams. It was titrated with N/20 KOH volumetric solution and found to have a free acid value of 2.63, and a saponification value of 223.

The fatty acid was liberated from the saponification mixture by heating with an excess of hydrochloric acid, cooled, the solid fatty acid filtered off and dissolved in chloroform. It was washed free of hydrochloric acid and evaporated to dryness. The residue was taken up with ether, dried with anhydrous sodium sulfate, filtered and evaporated to dryness. The residue, 2.0780 grams, was dissolved in neutral alcohol by the aid of heat. It was refluxed with a measured excess of N/2 KOH volumetric solution and the excess alkali back titrated with N/2 HCl volumetric solution. The fatty acid residue had a neutralization value of 242. Myristic acid (9) has a neutralization value of 246.1; palmitic acid (10) 219.1. Therefore, the distillate No. 1 was believed to contain largely myristic acid.

The distilling range 83-150 degrees, with the temperature rapidly moving through this range (pressure 3 mm.) indicates the probability of other lower members of the saturated fatty acid series. These members were not isolated due to the limited amount of material in this fraction.

Distillate No. 1a, distilling at 150-176 degrees under 3 mm. pressure, amounted to 32.3 grams. This fraction solidified at 17-19 degrees C. Two samples, of 1.4196 and 1.4210 grams respectively, had a saponification value of 236, using a measured excess of N/2 KOH alcoholic volumetric solution and back titrating the excess alkali with alcoholic N/2 HCl V. S. Methyl myristate has a saponification value of 231.6 (11).

The fatty acid was liberated from the saponification mixture by heating with an excess of hydrochloric acid, the mixture cooled, and the solid acid filtered off, dissolved in chloroform, washed with water, and evaporated to dryness. The acid was then recrystallized repeatedly from methyl alcohol until a constant melting point of 52.5-53.5 degrees was obtained. An authentic sample of myristic acid from the Eastman Kodak Company melted at 52.5-53.5 degrees C., and no depression of the melting point of the mixed samples was noted.

A sample of 0.228 gram of the fatty acid had a neutralization value of 260, equivalent to a molecular weight of 215. Myristic

acid (9) has a neutralization value of 246, and a molecular weight of 228. The isolated compound was characterized as myristic acid.

Palmitic Acid

The distillate No. 2 of the methyl esters of the saturated fatty acids, distilling 176-200 degrees C., at 3 mm. pressure, amounted to 20.3 grams. Most of this fraction distilled 188-200 degrees C. This fraction was repeatedly recrystallized from methyl alcohol. The saponification value of the ester was found to be 203.7; methyl palmitate has a saponification value of 207.6 (12). The ester was then saponified and the free fatty acid obtained as noted for myristic acid. The free acid was recrystallized from ethyl alcohol and acetone until the melting point was constant at 61-62 degrees. Palmitic acid melts at 62.6 degrees C. (13).

Acid From Distillate No. 3

This fraction amounted to 6 grams and distilled 185-222 degrees C., at 4 mm. pressure. Saponification value of the ester was found to be 191, using 0.5 and 2.0 gram samples. This ester was impure.

The acid was recovered from the saponification mixtures by refluxing with concentrated hydrochloric acid, the alcohol recovered and the acid allowed to solidify by cooling. This solid acid was filtered off, washed and recrystallized successively from acetic acid, methyl alcohol, absolute alcohol, and benzene, until the melting point was constant at 75-76 degrees C. Titrated with N/20 KOH, using petroleum ether to dissolve the fatty acid, the neutralization values of 149 and 142 were obtained, equivalent to molecular weight of 377 and 394, using 0.2 and 0.1 gram samples respectively. The methyl ester was then recrystallized from alcohol and a saponification value of 151 was found, using a 1.1883 gram sample. Calculation of the saponification value of $C_{23}H_{47}COOCH_3$ gives 146.7; $C_{23}H_{47}COOH$ (14) has a molecular weight of 368 and a neutralization value of 152. Grün (15) states the melting point of this acid (lignoceric) is 80.5 degrees C. However, this acid isolated from distillate No. 3 is not definitely characterized due to insufficient amount of material and the lack of reliable information on the higher fatty acids as found in the current literature.

Cerotic Acid

The No. 4 distillate of the distilled methyl esters of the saturated fatty acids was purified by repeated recrystallizations from 95 per cent. alcohol. The melting point of this fraction, finally, was 60-61 degrees C., and the saponification value was found to be 126, using two 1-gram samples and alcoholic

N/2 KOH and back titrating with aqueous N/2 HCl volumetric solution. From the saponification value mixture the solvents were removed by the aid of the steam bath and the free acid liberated by refluxing with 10 cc. of concentrated HCl.

After cooling, the free fatty acid was filtered off, washed with distilled water and finally filtered on a suction filter, using a small amount of absolute EtOH to remove the last traces of water. It was then recrystallized from ethyl acetate and finally from toluene, by dissolving with the aid of heat and allowing to crystallize at 0-5 degrees C. By such repeated recrystallizations the melting point was raised from 66 degrees to 78 degrees C. The melting point of 78 degrees C. was obtained on material dried over KOH and $CaCl_2$ for two days, under water-pump vacuum. This melting point is 1 degree to 1.5 degrees C. lower than that obtained for cerotic acid from Chinese Insect Wax, but is strongly indicative of this acid being present.

A sample of 0.2430 gram of this acid (from *Achillea Millefolium* L.) had a neutralization value of 138, equivalent to a molecular weight of 405: $C_{25}H_{51}COOH$ has a calculated neutralization value of 141 and a calculated molecular weight of 396.42.

Retort Residue The residue left in the retort, after distillation of the methyl esters, was a dark color and of a waxy consistency. Decomposition of the original material seemed to have occurred and therefore no investigation was made of it.

Triacontane The portion of the non-saponifiable treated with acetic anhydride and bromine was divided roughly into that relatively insoluble and relatively more soluble in the acetic anhydride. The portion insoluble was dissolved in 2000 cc. of alcohol (95 per cent.) by the aid of heat, cooled and filtered. The part insoluble on cooling was then repeatedly recrystallized successively from alcohol (95 per cent.), ethyl acetate, chloroform, acetone, toluene, and from absolute alcohol until a constant melting point of 65 degrees C. was obtained.

The sample was then tested for sterols (16) and found to be sterol free. It was then treated with hot concentrated sulfuric acid and was found to be stable and not charred. Therefore, the substance was characterized as a hydrocarbon.

Triacontane (17) melts at 65.6 degrees C. The substance from *Achillea Millefolium* L. was definitely characterized as Triacontane.

Ceryl Alcohol

A portion of the non-saponifiable material was repeatedly recrystallized from 95 per cent. and absolute alcohol, and from benzene until a constant melting point of 79-80 degrees C. was obtained. Ceryl alcohol (18) from Chinese Insect Wax mixed with the above purified material showed no depression of the melting point.

The acetate was prepared by refluxing the above with acetic anhydride, during thirty minutes, the excess acetic anhydride evaporated off and the residue repeatedly recrystallized from benzene until the melting point became constant at 63-64 degrees C. The ceryl acetate (18) prepared from Chinese Insect Wax ceryl alcohol melted at 64 degrees C. Sterols were absent (16). The material charred under the influence of sulfuric acid (conc.).

This non-saponifiable substance from *Achillea Millefolium* L. was characterized as Ceryl Alcohol (19).

Sterol

The non-saponifiable material amounted to 182 grams. It was originally determined to use the digitonide method for isolating the sterol from this material. No digitonin was available for some time so most of the non-saponifiable material was treated with acetic anhydride and bromine for isolation of the hydrocarbon.

Three grams of the remaining portion of the non-saponifiable material was treated with digitonin according to the method of Fritzsche (20). This 3-gram portion was dissolved in 150 cc. of 95 per cent. alcohol, heated to 65 degrees C. and then 250 cc. of a 1 per cent. digitonin solution (at 65 degrees C.) was added gradually and with stirring to the non-saponifiable solution. The precipitate was filtered off the next day, washed with ether, the sterol extracted by xylene and then repeatedly recrystallized from alcohol (95 per cent.) and absolute alcohol, until a constant melting point of 135 degrees C. was obtained.

The sterol reacted positively to the Liebermann-Buchard (16) color reaction test for sterols, when compared simultaneously with a known sample of cholesterol.

(1) Lewkowitsch, J.: Chemical Technology and Analysis of Oils, Fats and Waxes, 6 ed. (1921), v. 1, p. 554.
(2) *Ibid.*, p. 581.
(3) *Ibid.*, pp. 201, 584.
(4) Stepanow, A.: Berichte der deutschen Chemischen Gesellschaft (1906), 39, pp. 4056-57.
(5) Lewkowitsch, J.: Chemical Technology and Analysis of Oils, Fats and Waxes, 6 ed. (1921), v. 1, p. 554.

(6) Rosenthaler, L.: Der Nachweiss organischer Verbindungen (1914), p. 306.
(7) Rosenthaler, L.: Grundzuge der Chemischer Pflanzenuntersuchung (1928), 3 ed. p. 66.
(8) Kamm, O.: Qualitative Organic Analysis (1922), 1 ed., p. 142.
(9) Lewkowitsch, J., Chemical Technology and Analysis of Oils. Fats and Waxes, 6 ed., v. 1, p. 524 (1921).
(10) *Ibid.*
(11) Calculated from $C_{13}H_{27}COOCH_3$.
(12) Calculated from $C_{15}H_{31}COOCH_3$.
(13) Lewkowitsch, J.: Chemical Technology and Analysis of Oils, Fats and Waxes (1921), 6 ed., v. 1, p. 162.
(14) Grün, A.: Analyse der Fette und Wachse (1929), v. 1, p. 143.
(15) *Ibid.*, p. 112.
(16) Mathews, A. P.: Physiological Chemistry (1921), 3 ed., p. 82.
(17) Gascard, A.: Annales de Chimie (1921), 15, p. 342.
(18) McMurray, R. L.: Unpublished work on Chinese Insect Wax (1931).
(19) Lewkowitsch, J.: Chemical Technology and Analysis of Oils, Fats and Waxes (1921), 6 ed. v. 1, pp. 245, 440, 617.
(20) Rosenthaler, L.: Grundzuge der Chemischen Pflanzenuntersuchung (1928), 3 ed., p. 62.

Summary

1. The percentage of petroleum ether soluble extractive amounted to 2.019 per cent. using 100 pounds of air dried, ground blossoms in a Lloyd Extractor.

2. Organic compounds isolated from this extract and not previously reported in the literature are:

(a) Fatty acids—saturated
- Myristic acid 1
- Palmitic acid 2
- Undetermined acid 3
- Cerotic acid 4

(b) Fatty acids—unsaturated
- Linoleic acid 5
- Oleic acid 6

(c) Alcohol—saturated
- Ceryl alcohol 7

(d) Alcohol—unsaturated
- Sterol 8

(e) Hydrocarbon—saturated
- Triacontane 9

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The author wishes to express his thanks and appreciation to Professor W. O. Richtmann and the other members of the faculty of the Department of Pharmacy of the University of Wisconsin.

RECENT DEVELOPMENTS IN PHARMACOPŒIAL VITAMIN STANDARDIZATION

By Professor E. Fullerton Cook*

DURING the revision of the U. S. P. X it became apparent that the newly discovered, fat-soluble vitamin A should be recognized as an important factor in the potency of Cod Liver Oil. It was also being demonstrated that there was another substance spoken of as "the antirachitic factor" which should be given consideration, but it had not then been sufficiently studied to know how to evaluate it. However, a group of those active in developing vitamin knowledge, including Doctors Hess, Sherman, McCollum, Anderson and Holmes, were invited by the Pharmacopoeia Committee to suggest the basis for the new U. S. P. text and they developed the first standard Vitamin A assay method (1924) (See U. S. P. X, page 263) and this is still essentially correct. In setting a Vitamin A standard for Cod Liver Oil this group of early workers realized that no one then knew what was the potency of an "average oil", so they only required a minimum amount (50 units), primarily to exclude the Cod Liver Oils then on the market which were being purified and bleached by chemical methods and thereby destroying all vitamins.

In the period following 1926, when the U. S. P. X became official, the scientific knowledge concerning vitamins advanced rapidly so that in 1930 it was realized that the U. S. P. standards were entirely inadequate and steps were taken to issue a new text by "interim revision."

The U. S. P. Board of Trustees appropriated an initial $1000.00 toward the expense and a "Pharmacopœial Vitamin Committee" was organized and the first meeting called in New York City. At that meeting were present representatives of the Vitamin Laboratory of the Food and Drug Administration at Washington, representatives of the National Institute of Health (Public Health Service) at Washington, leading authorities in the new Vitamin Science, including Doctors McCollum, Mendel, Sherman, Hess, Steenbock, Dutcher, Fine, Holmes, Jones (of Philadelphia), Kohman of Washington, Mitchell of Cincinnati, also representatives of the scientific staffs of many of the important pharmaceutical houses in this country. The meeting was conducted under the auspices of the U. S. P. Committee of Revision and presided over by the Chairman of that Committee.

*Chairman of the Revision Committee of the U. S. Pharmacopœia.

The Conference agreed upon the general methods of assay for Vitamins A and D, adopting in the main the details which had already been carefully developed by a Vitamin Committee of the American Drug Manufacturer's Association under the Chairmanship of Dr. Arthur D. Holmes. The Committee adjourned after a full day of discussion, having reached practically a unanimous agreement of all points. The Committee also appointed Doctors McCollum and Steenbock as their representatives at the International Vitamin Conference called in London by the Health Organization of the League of Nations.

Some months later, the London Conference having been held and its deliberations and conclusions released, a second meeting of the U. S. P. Vitamin Committee was called in New York, again with a large group participating, about thirty-five in number. Again the Government representatives, the leading experts in the vitamin sciences in this country and members of the scientific staffs of pharmaceutical manufacturers were present at the invitation of the Pharmacopœia. At this meeting all discussions were subsequently reproduced stenographically for the benefit of those who were present and for the information of other vitamin experts in this country and abroad, a number of foreign vitamin authorities having accepted membership on the Committee.

Again the Committee agreed upon many points, perhaps the most important being the recommendation that the U. S. P. adopt as its standards the "International Vitamin Units".

To carry out the decisions of the larger Committee, and to specifically serve as an advisory group for the Pharmacopœia, the U. S. P. Board of Trustees now established "The U. S. P. Vitamin Advisory Board" and appointed the following members:

Dr. Lafayette B. Mendel of Yale University,
Dr. H. C. Sherman of Columbia University,
Dr. E. M. Nelson, Director of the Vitamin Laboratory of the Food and Drug Administration,
Professor E. F. Kelly (representing the Trustees),
E. Fullerton Cook (representing the U. S. P. Committee of Revision).

The International Standards

By this time the Health Committee of the League of Nations had released and sent to this country a limited amount of the "International

Vitamin A Standard" in the form of "Carotene" and the International Vitamin D Standard, a special "Irradiated Ergosterol", both of these having been prepared at the "British Institute for Medical Research" under the direction of Sir Henry Dale.

The U. S. P. Reference Cod Liver Oil of Known Vitamin A and Vitamin D Potency Expressed in the New U. S. P. Units (International Units)

There being only a limited amount of this International Standard available the Vitamin Board immediately undertook the preparation of a sufficient quantity of a Cod Liver Oil of known vitamin potency to be used as the basis for the standardization of American medicines and foods claiming "A" or "D" vitamin potency.

The Vitamin Board secured the co-operation of the Bureau of Fisheries at Washington who supplied a sufficient quantity of authentic Cod Liver Oil, collected and destearinated under the supervision of the Government Laboratory in Gloucester, Massachusetts. This oil was immediately placed in 30 cc. amber-colored glass containers under rigid conditions involving the drying of the container and oil to eliminate all water, the exclusion of all air by vacuum, the introduction of carbon dioxide and hermetic sealing, independent of the screw cap.

This packaged oil was immediately placed in cold storage at a temperature under 15° C. Previous experience had shown that under such treatment and storage no deterioration in Cod Liver Oil could be detected over a long period of time. Nevertheless the plans of the Vitamin Board include a re-assay of this oil every six months for both its Vitamin A and Vitamin D potency.

To determine the initial vitamin activity of the "Reference or Standard Cod Liver Oil" the Board then arranged with seventeen Vitamin Laboratories to assay this bottled oil, following exactly the assay methods adopted by the large Vitamin Committee. The Board supplied added information made available by the International Vitamin Committee and supplied uniform report blanks including graphs. All laboratories reported only by code number, the Chairman of the Board alone holding the key.

One set of assays was arranged for in London in the laboratory of Doctor Coward, another in Oslo, Norway, under Dr. Poulsson at the National Vitamin Laboratory, another at Johns Hopkins, another at Columbia University, another at the University of Wisconsin and

the others by well-known vitamin experts, many of them directing commercial laboratories. The Board paid for two of these assays and all others were voluntary. When it is realized that the average cost of a Vitamin A assay is $280.00 and a Vitamin D assay $80.00 and many laboratories ran from two to five assays on this one sample, the extent and value of this co-operation can be estimated.

Another feature of the program which is of outstanding significance is the fact that when the new U. S. P. Vitamin Standards and Assay Methods are issued, most of the important vitamin laboratories in this country and even in producing countries abroad are already thoroughly familiar with the details of the New U. S. P. Assay.

Fifteen of the seventeen laboratories have already reported and the other two have the assays under way. The Vitamin Board has painstakingly studied and evaluated the reports and have recommended the following standards for the official Cod Liver Oil:

Minimum Standard for Vitamin A for U. S. P. Cod Liver Oil. The minimum Vitamin A standard for U. S. P. Cod Liver Oil shall be not less than 600 International Units.

Minimum Standard for U. S. P. for Vitamin D Cod Liver Oil. The minimum Vitamin D standard for U. S. P. Cod Liver Oil shall be not less than eighty-five International Units.

> *Note: The new "U. S. P. Vitamin Units" and "U. S. P. Vitamin D Units" are identical with the corresponding "International Units".* In expressing on labels the potency of vitamin-containing products, it is recommended that the term "U. S. P. Vitamin A Units" or "U. S. P. Vitamin D Units" be employed. To indicate the adoption of the *new* standards the statement "U. S. P. X—Revised 1934" may be used.

For the benefit of manufacturers or others who wish to know the approximate relationship between units they are now using and International Units of Vitamins A and D, the following information is provided:

One U. S. P. X Sherman or A. D. M. A. Unit of Vitamin A equals 1.4 International or new U. S. P. Units.

One Steenbock Unit of Vitamin D equals 2.7 International or new U. S. P. Units.

One International or U. S. P. Unit of Vitamin D equals 3.25 A. D. M. A. Units.

The U. S. P. Board of Trustees has also announced the release of the "Reference Cod Liver Oil", prepared under the supervision of the Vitamin Board, for use in the standardization of medicinal or food products claiming vitamin potency and already many laboratories in this country have secured this official vitamin standard. These new U. S. P. Standards of Vitamins A and D will be the basis for the evaluation by the Food and Drug Administration of all products in the country claiming Vitamin A or D potency.

THE COSMETIC SPLURGE—The Tugwell bill may not be enacted exactly as proposed but it will certainly have plenty of territory to cover, especially in the cosmetic fields; that is if the figures of the National Beauty Institute of Chicago mean anything. They tell us that the average American woman spends one hour a day or 365 hours a year in front of the mirror and expends an average of $25 each year for cosmetics, treatments and other beauty aids. The figure embraces all women fifteen years old and over.

American women annually consume 100,000,000 pounds of cold cream, 50,000,000 pounds of fancy face creams, 52,000,000 pounds of skin lotions, 18,000,000 pounds of toilet soap, 12,000,000 pounds of bath salts, 8,000,000 pounds of face powder and 4,000,000 pounds of rouge, and lipstick. The total bill of the American woman for cosmetics alone is approximately $375,000,000.

The JOURNAL regretfully announces the death, recently, of three valued members of the Board of Trustees of the Philadelphia College of Pharmacy and Science.

Joseph W. England, Chairman of the Board and a member of the Publication Committee of this JOURNAL, since 1893.

Walter V. Smith, prominent wholesale druggist.

Philip H. Johnson, noted architect and a friend of the College.

Memoirs will appear in the January issue.

THE MICROSCOPE IN THE PHARMACY

By Louis Gershenfeld, B. Sc., P. D.*

THE MICROSCOPE derives its name from the two Greek words, "mikros," meaning small, and "skopeo," to see. The first inventions of an instrument of this type were the simple microscopes, practically similar to the well-known magnifying glasses with their convex lenses. Zacharias Jansens, a Dutch optician, is credited with having presented the simple microscope to the public in the year 1590, though evidence is available that magnifying lenses were in use centuries before the period of classical Greece.

It is not the purpose of this article to give a detailed history of the microscope and microscopy. It therefore will be sufficient merely to state that the magnifying lens or simple microscope is not used extensively today in scientific laboratories. This instrument has been replaced by the compound microscope. The latter originated in the seventeenth century, and the actual inventor is not known. Dr. Robert Hooke (1635-1703), a mechanical genius who anticipated many modern discoveries and inventions, gives a detailed description of the compound microscope used by him in examining plants and metals and reported by him in his "Micrographia" (London, 1665).

The Jesuit's priest, Athanasius Kircher (1602-80), of Fulda, was probably the first to employ the microscope (only a 32-power instrument) in investigating the causes of disease (see his "Scrutinium pestis," 1658). Marcello Malpighi (1628-1694), distinguished Italian biologist and anatomist, and the founder of histology, was one of the greatest of the early microscopists.

Another very great microscopist of this period was Antonj van Leeuwenhoek (1632-1723), of Delft, who, as a careful and most thorough worker, added considerably to the scientific knowledge of the day. Eustachio Divini in 1668, Philip Bonnani in 1698, and even Sir Isaac Newton in 1672, described microscopes used by them.

Before leaving these early microscopists who laid the foundation of microscopy and in turn of many branches of science, some brief remarks should be made concerning Jan Swammerdam (1637-80), of Holland, whose short life was crowded with so much interest and the

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presentation of information of value to science and mankind. His biographer, Herman Boerhaave (1668-1738), famous as a teacher, chemist and practitioner of medicine, who published the "Bybel der Natuur" in 1737, after the death of Swammerdam, tells us that the latter was a scientific enthusiast and a man of great reserve, who cared little whether or not the world at large knew of his work.

Jan Swammerdam's interest in natural history was aroused and developed in his father's apothecary shop, where the finest collection of exotic fauna in Amsterdam was to be found. It was here he became expert in microscopic dissecting long before he began the study of medicine. In fact, he became so interested in the zoologic specimens among which he had grown up that he never practiced his profession but devoted his splendid labors to minute anatomy and embryology.

In the above work are to be found over fifty plates with accurate life histories and details of the finer anatomy of the bee, the snail, the clam, the squid, the frog and the May fly. The drawings in this collection surpass in exquisite delicacy and in accuracy of detail all other contemporary work. In 1658, Swammerdam discovered the red blood-corpuscles in the blood of the frog, but this was not publicly announced until after his death.

Malpighi described the red blood-corpuscles in 1665, seven years later, and due to priority of publication he is given the credit for this discovery by many workers. Swammerdam, a keen student of zoology, was also a capable experimental physiologist and anatomist.

The life of this man brought up in the environment of an apothecary shop is indeed well worth reading. He first, as an amateur, took an intelligent interest in microscopy and later aided in the solving of many scientific problems. (See W. Stirling's, "Some Apostles of Physiology," London, 1902; and Herman Klencke's, "Swammerdam oder die Offenbarung der Natur.")

Knowledge of the existence of micro-organisms, cellular elements, and many other scientific data known today was, of necessity, forced to await the discovery and perfection of instruments of magnification. The microscope is one of the most valuable instruments in science today and serves those interested in microscopy as the telescope serves the astronomer. Broadly speaking, the development of all of the biological sciences and many of the others have developed hand in hand with the discovery of the compound microscope and the improvement in the latter and with the advancement and improvement in microscop-

ical technique. But little progress in embryology, histology, pathology, bacteriology, and in other branches of science, was possible without the microscope.

It was in 1847 when Matthias Jacob Schleiden (1804-81), the eminent Hamburg botanist, used the microscope in examining the sarsaparillas, that this instrument was first employed in the examination of drugs. In 1851, Professor Pereira in his introductory lecture on Materia Medica before the Pharmaceutical Society of Great Britain remarked, "You are doubtless conversant with the recent very extensive employment of the microscope for disclosing the adulteration of food. No less useful—no less powerful—is it in disclosing the contamination of drugs; and I cannot too strenuously recommend you to employ it." In 1853, Schacht revealed the value of the compound microscope in the identification and differentiation of textile fibers.

A century ago there were to be found but twelve compound microscopes in America. About sixty years ago (in 1874) Edward Bausch (later of Bausch & Lomb) completed the manufacture of the first microscope in the western hemisphere. Thus there was announced to the universe that the new world was ready to do its share in the development and progress of science. A half century ago there were no research laboratories in North and South America; but few college laboratories were to be found in the United States, and the compound microscope, a most expensive instrument, was (if at all) only to be found in the possession of a few of the professors and rich scientists. An inventory today would record hundreds of thousands of these instruments in use in the western hemisphere.

It is interesting to note that in January, 1852, an article entitled, "On the Microscope, as a Means of Detecting the Admixture or Adulteration of Drugs," appeared in *Annals of Pharmacy,* and this was reprinted in the AMERICAN JOURNAL OF PHARMACY, Vol. XXV, pages 45-48, 1853, published by the Philadelphia College of Pharmacy. In this article the use of the microscope in the examination of drugs is discussed and its value was even then appreciated.

Now, what are the branches of science with which the pharmacist is engaged and in which microscopy and microscopical technique are encountered? Let us briefly review, first, his college training. Microscopic botany (or vegetable histology), pharmacognosy, physiology, bacteriology, biochemistry, and chemistry, and in some instances zoology, are branches of science in which laboratory work and micros-

copy are given in the recognized colleges of pharmacy to those studying pharmacy. A graduate completing the latter course can, with his microscope, place himself in a position to appreciate the work of the biologist, bacteriologist, mineralogist, and he can improve his own standing in his community because his microscope can reveal to him a greater knowledge of his drugs and his preparations.

With additional study and application, a pharmacist can extend his service to help the physician and the public health worker by establishing in his pharmacy a clinical laboratory. In the latter, bacteriological, parasitological, hematological, toxicological, immunological and clinical chemical tests are performed and in which specific fields a pharmacist can train himself. All of these branches of science require the aid of the microscope.

It is really surprising to observe the comparatively small number of pharmacists who possess a microscope or are interested in using it. Even if only for the occasional examination of crude drugs or powdered drugs or spices, this instrument should be available.

Pharmacists say that they deal with reputable houses. Some do and some don't; and even then the retail phramacist cannot shift his responsibility to a wholesaler for, after all, the main responsibility in selling and dispensing pure drugs and preparations rests with him. Other pharmacists claim that the cost of the examination of drugs microscopically would be out of proportion to the profits accrued. Yet, on the other hand, even a minor mistake in the sale of some crude or powdered drug may result in a considerable loss of trade, out of proportion to the error involved.

Adulteration of foods, spices, drugs, etc., is still common in countries in which standards of purity do not exist or which are not strictly enforced by laws that may exist. A pharmacist known to exercise care in the selection of his drugs and spices would be patronized not only by the medical profession but also by the general public. Detection of adulteration is most frequently only possible by the use of the microscope and at times aided by microchemical technique. In fact, in the case of powdered drugs, the only important means of identifying the latter and detecting adulteration is by microscopic methods. Powdering destroys practically all means of microscopical (gross) identification of a drug, though occasionally color, odor and taste may be of some aid.

A chemical test may indicate the presence of starch, but it cannot reveal the particular kind of starch. The microscope is required to distinguish the different starches. A chemical analysis may reveal an abnormal amount of crude fiber, but only the microscope will show whether or not it is sawdust, ground nut shells or something else. The detection of adulteration not only in drugs but in many classes of food products is, at times, only possible by the microscope. In many instances, more actual information is obtainable by a microscopical examination than by a chemical analysis.

Microchemical tests are also of considerable aid for the identification and detection of impurities in drugs and chemicals and for the identification of plant constituents as well as for the detection of poisons and vegetable adulterants. Even in chemistry the microscope is being employed for distinguishing the forms of minute crystals, determining their true character; and such analyses in mixtures of substances are frequently carried out with less time consumed than would be required by chemical methods.

Chemical microscopy is becoming of greater and greater importance to the chemist, the toxicologist, the mineralogist, the metallurgist, the scientist working in the textile industry, and in the examination of pulp woods and paper, and even in the detection of crime.

I have personally used a microscope and I know others have to observe whether or not the proper degree of subdivision of the active ingredient in an ointment has been obtained. Mercurial ointment may be cited as an example. The microscopy and microchemical reactions of the many alkaloids found on the shelves of the average pharmacy is a most interesting subject. Chemical microscopy has accomplished wonders. Of course, if clinical work is being conducted, and it can readily be in conjunction with any professional pharmacy, microscopy must be made available. The examination of urinary sediments, feces for ova and parasites, blood for many different observations, bacteriological investigations and even in public health work and in sanitary investigations where water, milk and foods are being examined for their purity, the microscope is needed.

I have briefly outlined the service that the microscope can give to the wide-awake pharmacist in his own work. Mention was made of some of the other problems which can be aided by this instrument. The pharmacist who will give the subject of microscopy some serious attention will find the latter will pay him dividends even in terms of

financial gain. But what is as important is the fact that microscopy can be a splendid means of unfolding to him many new aspects of other branches of science and of this wonder world in which we live.

The inquiring pharmacist will find it both fascinating and instructive; and who knows but just as Swammerdam did, he or his children interested in microscopy may even help in the solving of some scientific problem or lay the foundation for some scientific fact which is both instructive and fascinating.

In conclusion, may I say that those unfamiliar with the microscope and microtechnique are frequently afflicted with "stage fright" and do not realize that the proper use of the microscope can be easily acquired by systematic knowledge, study and application. They will find that the actual manipulation of the microscope is no more difficult than using opera glasses; and study and perseverance, aided later by experience, will enable them to acquire microtechnique.

THE FIRST ADHESIVE PLASTER—Many people are not aware that the first India rubber plaster was made in Milltown. This plaster was invented in 1852. The first adhesive plaster was used 400 years before Christ, and its type is still being used. It was known as the Daichylon type of plaster. The latest plaster is the zinc oxide rubber devised by Johnson and Johnson.

THE SOPORIFIC SPONGE—Before ether was discovered in 1846 and through the years prior to the nineteenth century the soporific sponge was used to deaden the pain of surgical operations. The sponge was dipped in solutions of opium, belladonna and other narcotics, and was applied to the part operated on.

ABSTRACTED AND REPRINTED ARTICLE

PHARMACIST'S LIABILITY FOR NEGLIGENCE IN FILLING PRESCRIPTIONS*

By Lorenz J. Brosnan, Esq.

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THE LAW imposes upon a pharmacist a very high degree of care. Not only is he under a duty to fill a prescription correctly, but he is under the further obligation in cases where he is not certain of the exact meaning of the prescription, to inquire from the prescribing physician as to the contents thereof. A case illustrating the latter principle in which a pharmacist was held accountable for negligence, was the subject of recent review by an appellate court in one of our mid-western States.

A certain Mrs. Jones called in her family physician to attend her for her complaints of a dull pain in her arm. The doctor examined her, decided the trouble was muscular rheumatism and wrote out the following signed prescription: "Strontium Salicylate four ounces (Wyatt), teaspoonful in water four times a day." A relative of the patient took this prescription to a drug store at about noon and left the same with a drug clerk who told him to call later for it. He stopped by in the afternoon and the medicine was not ready. It actually was delivered to the patient's relative in the early evening, and a dose of the medicine was promptly taken by the patient. She soon became very sleepy and went to bed. During the night she was given three additional doses and she went into a state of coma. Her breathing became slow and labored, and her pulse slow. The next morning, when her doctor called, he realized something had gone wong and he undertook to eliminate the drug from her body. She remained unconscious for about two days, and when she did improve she went through a severe and prolonged siege of disorders and distresses of her entire system.

It was ascertained, and not denied by the druggists, that the medicine that had been put up consisted of pure strontium salicylate, manufactured by Parke-Davis & Company, and that the patient had taken

*Reprinted from the *New York State Journal of Medicine* (Sept., 1933).

into her system within sixteen hours about seven hundred and twenty grains of the drug.

Suit was instituted by the woman to recover large damages against the drug company, charging it with having negligently or improperly filled the prescription. The case went to trial and a verdict was found by the jury in favor of the plaintiff and against the drug company.

Upon the trial, the testimony indicated that the substance strontium salicylate, of which seven hundred and twenty grains had been taken in so short a time, is dangerous in doses of more than about sixty grains a day. The drug, according to the testimony, is a combination including salicylic acid which is used as a corn cure by application so it will eat away the tissue of the corn and soften it. The testimony was that the prescription as filled would irritate the stomach and intestines, cause ringing in the ears, disturb vision, cause dilation of blood vessels and inflammation of the kidneys, and other dangerous effects, and that even death could be produced by it.

Upon the trial, the testimony centered upon what was the proper handling by a competent druggist of a prescription worded as the one in question. The doctor had put after the drug required the word "(Wyatt)," which word may have been intended as a reference to John Wyeth & Brother, the well-known pharmaceutical manufacturing company. According to the evidence, neither the Wyeth Company nor any of the other well-known manufacturing chemists, except Parke-Davis & Company, put pure strontium salicylate upon the market. The Wyeth Company, however, did put out a certain effervescent strontium salicylate compound, composed of about 10 per cent. of that drug. According to the testimony, a teaspoonful of the Parke-Davis product was ten or twelve times as powerful as the Wyeth compound.

The defense of the case was conducted on the theory that it was necessary to fill a prescription literally and that had been done in this case. On cross-examination, however, the defendant's own witnesses made clear that a careful pharmacist would have found it impossible to fill such a prescription accurately without consulting the doctor who made it out, to check the meaning of the word "Wyatt." One of the defense witnesses, when asked what he understood "Wyatt" in a prescription to mean, answered, "Well, I would say it would mean John Wyeth & Bro. or Sons."

The examination continued as follows:

"Q. If you were filling this prescription wouldn't you find out?

"A. Surely.

"Q. You would find out?

"A. Yes.

"Q. And if you found that this effervescent strontium salicylate was the only one made by Wyeth and this prescription contains strontium salicylate Wyatt, there might be a question in your mind as to whether this was called for or something else?

"A. Well, there is a question in every prescription.

"Q. There is a question in every prescription?

"A. Yes.

"Q. Why is there a question in every prescription?

"A. Sometimes it isn't definitely written or definitely prescribed.

"Q. When you can't read a prescription correctly you take chances and consult the pharmacopœia to see.

"A. If we can't read it correctly we call the doctor.

"Q. Is there a strontium salicylate Wyatt?

"A. No.

"Q. There is not. Then it couldn't be filled according to the prescription?

"A. The manufacturer doesn't——

"Q. It could not be filled according to the prescription?

"A. Say so, if you want to.

"Q. This calls for strontium salicylate manufactured by Wyatt?

"A. There isn't such a manufacturer according to the spelling of the prescription there.

"Q. If you received this prescription over the desk in your drug store you would know what was meant by that, wouldn't you?

"A. Not necessarily."

Another of the defense witnesses on cross-examination gave the following testimony:

"Q. Suppose that prescription came to you, what would you take the word (Wyatt) to mean?

"A. Probably meant Wyeth.

"Q. Wyeth & Bro.?

"A. Wyeth & Bro.

"Q. Pharmaceutical manufacturers, are they?

"A. Yes, sir.

"Q. That is what you would take it for, wouldn't you?

"A. Yes, sir.

"Q. Have you a right when a doctor prescribes a particular kind of drug, when you find the doctor has made a mistake, to substitute something else in place of that?

"A. No."

From the judgment of the trial court, the defendant drug company took an appeal and the higher court affirmed the judgment of the trial court, holding that liability was properly imposed upon the defendant. In its opinion the appellate court considered the theory of the defense in part as follows:

> "The defendant contends that 'the legal duty of a druggist to a purchaser can go no further than to dispense the identical substance which his prescription calls for.' No authority is cited by the defendant in support of this contention. In its brief it states: 'We have searched the books and have been unable to find a case similar to the one at bar.' The instant contention is primarily based upon the assumption that a pharmacist is obliged to fill any and all prescriptions. Such is not the law. As a chemist he may know that the physician has erred in his prescription and that to fill it might cause death or serious injury to the patient. The argument interposed, briefly stated, is this, that the proof shows that there was no such pharmaceutical manufacturer as Wyatt, and that therefore Z who filled the prescription had the right to disregard the word 'Wyatt' and to fill the prescription with pure strontium salicylate. It would be a sufficient answer to this contention to say that the jury were fully warranted, under all the evidence in this case, in finding that a competent and careful pharmacist would have understood what was meant by the word 'Wyatt.'"

The court further said:

> "If a prescription is doubtful as to what drug is really intended, it is the duty of the pharmacist to be alert to avoid a mistake, and if there is any reasonable doubt as to the identical thing ordered it is his duty to take all reasonable precaution to be certain that he does not sell one thing when another is called for. A contrary rule would tend to make a pharmacy a menace, instead of an aid, to suffering humanity."

In reading its conclusion to affirm the judgment against the drug company, the court quoted as follows from an earlier case, as a summary of the rules governing a druggist's liability for negligence:

> "Finally, in applying his knowledge and exercising care and diligence, the druggist is bound to give his patrons the benefit of his best judgment; for even in pharmacy there is a class of cases in which judgment and discretion must or may be exercised. The druggist is not necessarily responsible for the results of an error of judgment which is reconcilable and consistent with the exercise of ordinary skill and care. He does not absolutely guarantee that no error shall ever be committed in the discharge of his duties. It is conceivable that there might be an error or mistake on the

part of a qualified druggist which would not be held actionable negligence. But, while, as has been seen, the legal measure of the duty of druggists toward their patrons, as in all other relations of life, is properly expressed by the phrase 'ordinary care,' yet it must not be forgotten that it is 'ordinary care' with reference to that special and peculiar business. In determining what degree of prudence, vigilance and thoughtfulness will fill the requirements of 'ordinary care' in compounding medicines and filling prescriptions, it is necessary to consider the poisonous character of so many of the drugs with which the apothecary deals and the grave and fatal consequences which may follow the want of due care. In such a case 'ordinary care' calls for a degree of vigilance and prudence commensurate with the dangers involved. The general customer ordinarily has no definite knowledge concerning the numerous medicines and poisons specified in the U. S. Dispensatory and Pharmacopœia which registered apothecaries are by our statutes expressly allowed to keep, but must rely implicitly upon the druggist who holds himself out as one having the peculiar learning and skill and conceptions of legal duty necessary to a safe and proper discharge of that duty. 'Ordinary care' with reference to the business of the druggist must therefore be held to signify the highest practicable degree of prudence, thoughtfulness and vigilance and the most exact and reliable safeguards consistent with the reasonable conduct of the business, in order that human life may not consistently be exposed to the danger flowing from the substitution of deadly poisons for harmless medicine."

MEDICAL AND PHARMACEUTICAL NOTES

DINITROPHENOL, A STIMULANT OF METABOLISM—During the Great War the attention of physicians in France was directed to cases of poisoning in munition factories caused by dinitrophenol, an intermediate product in the manufacture of explosives. Many persons who handled this substance developed headache, dizziness, vomiting, and high fever, in a few cases with fatal results. As soon as the source of the trouble was traced prompt measures were taken to prevent such effects.

Dinitrophenol, $C_6H_3 \cdot (NO_2)_2OH$, is a derivative of phenol in which two atoms of hydrogen are replaced by NO_2 (picric acid is trinitrophenol). The variety known as alpha-dinitrophenol, or 2 : 4-dinitrophenol, has recently found therapeutic application. It is a yellow crystalline solid, slightly soluble in water, more so in alcohol and in ether. A 3 per cent. solution in water may be made by addition of half its weight of sodium bicarbonate. As a dye it is readily obtainable in pure form, being used as an indicator in pH estimations.

Within the past year alpha-dinitrophenol has been found to possess the property of augmenting the metabolism in doses which are relatively safe, a property which may give the drug important clinical applications. Cutting, Mehrtens, and Tainter (Stanford University, San Francisco) have shown by animal experiments that it causes an increase in the metabolism within one minute after injection, and somewhat more slowly when given by mouth. Clinical trials on a number of patients showed that a single dose of 3 to 5 mg. per kg. of body-weight given *per os* increased the basal metabolic rate from 20 to 30 per cent. in the first hour, the rate being maintained at this level for about twenty-four hours and not becoming normal until the third day. Daily doses of the same amount were given to six patients for periods varying from one to ten weeks, the B. M. R. being determined at regular intervals. By this means the rate was maintained at an average of 40 per cent. above the initial level, returning to normal in three or four days after discontinuance of the drug. All these patients lost weight without resort to dietary

restrictions, the maximum loss being 10 pounds in ten weeks. No deleterious effects were observed, such as are experienced with thyroid treatment. The only limiting factor is the fever caused by increased heat production, and for this reason the dose must be kept low and the results carefully watched.

In view of the many possible therapeutic applications of a drug possessing such properties, it is necessary to emphasize its limitations and possible dangers. It promises to be very serviceable in the treatment of myxoedema and of obesity, and it may find application in diabetes, but it must be remembered that excessive dosage and probably even long-continued administration may cause fever and other toxic manifestations. This property of producing pyrexia, if properly applied, might qualify it as a substitute for malaria treatment in neurosyphilis. So long, however, as its use is in the experimental stage, the drug must be employed with great caution and under strictly controlled conditions. In a report just to hand Anderson and colleagues (San Francisco) state that they used the drug in fourteen cases, in one of which a severe toxic reaction was encountered. The total amount given during fourteen days was 39.3 mg.-kg. (about 48 grains). The case was obviously one of idiosyncrasy, but such possibilities must be borne in mind.

Meanwhile attention has been drawn by Dodds and Pope (London and Cambridge Universities) to a similar nitro compound of cresol, dinitro-*o*-cresol. Experimental investigation has shown that the cresol compound has the same effect on the oxygen consumption of guinea-pigs as has the phenol compound, with about one-third of the dose. As regards toxicity both compounds appear to be of the same order.

Dinitro-orthocresol, $CH_3 . C_6H_2 . (NO_2)_2OH$, like the corresponding phenol compound, is a yellow crystalline dye. Cresol is methylphenol, and is known in three varieties—ortho-, meta-, and paracresol—metacresol being a liquid. Cresol, B. P., is a mixture of all three. (Through the *Prescriber*.)

Anderson, H. H., Reed, E. C., and Emerson, G. A. Toxicity of alpha-dinitrophenol. *J. A. M. A.*, 1933, Sept. 30, 1053-1055.

Cutting, W. C., Mehrtens, H. G., and Tainter, M. L. Actions and uses of dinitrophenol: promising metabolic applications. *J. A. M. A.*, 1933, July 15, 193-195.

Dodds, E. C., and Pope, W. J. Dinitro-*o*-cresol as a stimulator of metabolism. *Lancet*, 1933, Aug. 12, 352-353.

SODIUM TETRATHIONATE BETTER THAN METHYLENE BLUE FOR CYANIDE POISONING—Draize states that, according to results obtained in his laboratory, two of the various antidotes advocated to treat cyanide poisoning are effective. A dose of from 3 to 4 mg. of a hydrocyanic acid solution per kilogram of body weight is fatal for the rabbit when administered orally. The intravenous injection of from 2 to 3 cc. of a 2 per cent. solution of sodium tetrathionate per kilogram of body weight is effective in saving rabbits having received orally three times the minimal lethal dose of hydrocyanic acid. The sodium tetrathionate solution is administered with the onset of the first symptoms of cyanide poisoning. Rabbits tolerate three times the therapeutic quantity of sodium tetrathionate without exhibiting any toxic effects. Methylene blue administered intravenously in the form of a 1 per cent. aqueous solution does not afford as much protection. Rabbits receiving more than two times the minimal lethal dose could not be saved. The intravenous injection of quantities in excess of 2.5 cc. of a 1 per cent. solution of methylene blue was injurious to the rabbit. In the trial of sodium tetrathionate in carbon monoxide poisoning, rabbits were gassed to a point from which recovery was impossible without treatment. Sodium tetrathionate was more effective than methylene blue in reviving the poisoned animals.—*Science*, 78:131-152 (Aug. 18) 1933.

DERRIS ROOT, ASSAY OF—D. R. Koolhaas. (*Bull. Jardin. botan. de Buitenzorg.*, 12, 53, through *Pharm. Ztg. Berl.*, 1933, 78, 408.) The rotenone content of derris root varies considerably, from traces up to 12 per cent. Thick roots are generally richer than thin ones, the rotenone being mainly localized in the woody part of the root. The following process is given for the assay. Fifty gm. of the root, in No. 80 powder, and containing not more than 10 per cent. of water, is extracted in a Soxhlet apparatus for forty-eight hours with absolute ether. The ether solution, together with any rotenone that has separated out, is transferred to a 100 cc. centrifuge tube and concentrated to about 25 cc. If this solution is very viscous it is diluted with 10 cc. of ether. After standing for two days at ordinary temperature, and a further two days in the ice chest, the solution is centrifuged in an ice-cooled metal capsule for two to three minutes, and the liquor

is poured off. The crystalline mass is stirred up with 10 cc. of absolute ether, and after standing for one day in the ice chest, centrifuged off, dried for five to ten minutes at 80° C. *in vacuo,* and weighed. The melting point of the product is taken, and if under 120° C., the product is treated repeatedly with 10 cc. portions of ether until this melting point is attained. If, however, the melting point is over 163° C., then no rotenone is present.—*Quart. Jour. Pharm. Eng.*

SOLUTIONS FOR SPINAL ANALGESIA—The following formulas for solutions for producing spinal analgesia are taken from the new (twelfth) edition of the Pharmacopœia of the Manchester Royal Infirmary:—

Barker's Solution

Stovaine	0.10 gm.
Glucose	0.10 gm.
Distilled water	to 2 cc.

Duplas' Solution

Stovaine	0.06 gm.
Caffeine	0.10 gm.
Sodium benzoate	0.10 gm.
Distilled water	to 2 cc.

Chaput's Solution

Stovaine	0.10 gm.
Sodium chloride	0.10 gm.
Distilled water	to 1 cc.

Krœnig's Solution

Stovaine	0.08 gm.
Sodium chloride	0.0022 gm.
Distilled water	to 2 cc.

Chaput's Alcohol Solution

Stovaine	0.08 gm.
Alcohol	0.2 cc.
Distilled water	to 2 cc.

Tuffier's Solution

Stovaine	0.1 gm.
Sodium chloride	0.1 gm.
Distilled water	to 1 cc.

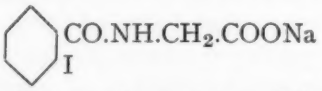
—*Pharm. Jour. Eng.*

HYDROGEN PEROXIDE, STABILIZATION OF—E. V. Christensen. (*Arch. Pharm. Chemi.*, 1933, 90, 227.) Among the substances which have been recommended as stabilizers of hydrogen peroxide may be mentioned alcohol, oxalic acid, tannic acid, benzoic acid, pyrogallol, nipagin, urea, barbituric acid derivatives, uric acid, acetanilide, phenacetin, quinine sulphate, and cinchonidine. Conflicting opinions are, however, often given for the efficiency of a particular compound. This is probably due to the influence of traces of impurities in the peroxide used. The new Danish Pharmacopœia requires a stabilizer to be added to the 3 per cent. solution of hydrogen peroxide, without specifying any particular one; the amount, however, is not to exceed 0.15 per cent. of stabilizer plus inorganic constituents. A comparative examination of the efficiencies of acetanilide, phenacetin, and diethylbarbituric acid, at concentrations of 0.1 per cent., was therefore undertaken. The results showed that of these only phenacetin was really effective in preventing the decomposition of a 3 per cent. solution of peroxide obtained by dilution of commercial 30 per cent. peroxide. Even when a trace of iron, manganese, or copper was added, the phenacetin still prevented any appreciable amount of decomposition.—*Quart. Jour. Pharm. Eng.*

"FOOD POISONING"—A PUBLIC HEALTH PROBLEM—J. C. Geiger and J. P. Gray (*American Journal of Public Health, 23*:1039, October, 1933) define food poisoning as the clinical syndrome resulting from the ingestion of food contaminated by certain types of bacteria. The etiology and epidemiology of food poisoning are fairly well understood, and with this knowedge it is possible to prevent outbreaks of this disease. But the control of food poisoning, as of other diseases, is hampered by delay in reporting, incomplete epidemiologic investigation and inadequate laboratory studies, incomplete preventive service and lack of rational legislation. Food poisoning is of two main types: 1, Botulism due to food contamination with *Clostridium botulinum* and its toxin, a disease of high fatality but comparatively rare; and 2, food poisoning due to organisms of the paratyphosus-enteritidis group, of much more frequent occurrence but low fatality. In the study of the epidemiology of food poisoning the determination of the particular food responsible is of first importance and secondarily the determination of the infecting organism by suitable lab-

oratory procedures. From a thorough study of each outbreak "something constructive can be gleaned and in turn practiced to prevent recurrence." Further control of food establishments is necessary including the examination of food handlers as possible carriers. As in the control of other diseases, education of practicing physicians, nurses, and the lay public as to the possibilities and dangers of food poisoning is important in the program of control.—Through *Long Island Medical Jour.*

HIPPURAN—Hippuran is a product of the Mallinckrodt Chemical Works, proposed by Swick for intravenous and for oral urography. Its chemical constitution is stated to be sodium ortho-iodohippurate.



Sodium ortho-iodohippurate contains 38.8 per cent. of iodine; it is said to be soluble in less than its own weight of water and to be stable in aqueous solution. It was chosen as a promising agent for visualizing the urinary tract, in view of the fact that hippuric acid normally occurs in the urine following the ingestion of benzoic acid, representing a conjugation of benzoic acid with glycine. Similarly, the ingestion of ortho-iodobenzoic acid is said to result in the appearance of ortho-iodohippuric acid in the urine.

BOOK REVIEWS

THE PHARMACEUTICAL POCKET BOOK FOR PRACTITIONERS AND STUDENTS. (Twelfth Edition.) Published by the Pharmaceutical Society of Great Britain, 17 Bloomsbury Square, London, W. C. I., at The Pharmaceutical Press, 23 Bloomsbury Square, London, W. C. I.

Since its introduction as the Pharmacists' Student's Pocket Note Book in 1906, this publication has appeared in various forms through eleven editions. The last edition was produced by the Science Committee of the society and published in 1925.

The book has always been extremely popular with practising pharmacists and pharmaceutical students as a compendium of useful information and work of easy reference for everyday use.

The section dealing with the Science and Art of Dispensing has been considerably enlarged and subsections dealing with tampons and sterilization have been included. In response to requests received by the Council of the Society for the British Pharmacopœia 1932 to be set out in imperial as well as metric proportions, the necessary conversions have been made.

Tables are included for the conversion of hydrometer readings into those of specific gravity, for the dilution of alcohol, of the proportions of active ingredients in official preparations of solubilities derived from authoritative sources and of specific gravities of chemicals and other substances. A comprehensive dictionary of synonyms and a veterinary posological table are also included.

The section of the book on Food and Diet has been entirely rewritten and considerably enlarged. A dietary for special diseases and conditions is now included.

Separate sections deal with the vitamins and endocrine substances and are written in the light of recent research.

The section on Urine Analysis has been revised by Dr. H. E. Archer and extended to include the examination of blood, gastric contents and urinary calculi.

The section on Poisoning deals with methods of treatment, antidotes, and medicinal and fatal doses. The last two are given in tabular form and the entire section has been rearranged with a view to speedy reference in case of emergency.

The size of page has been enlarged and type faces chosen to give a page which can be read with the minimum of effort, a matter of considerable importance in a book which contains a vast amount of information and must necessarily be printed in small type. The new edition is bound in flexible blue leatherette with gilt lettering.

The volume remains essentially a "pocket book" and its binding renders it capable of resisting the wear and tear of constant everyday use. For these reasons it is particularly valuable to the student and the practising pharmacist. At the same time its size and appearance make it worthy of a place in the library or on the pharmaceutical bookshelf.

The new Pharmaceutical Pocket Book is briefly an indispensable work of reference for all engaged or interested in pharmacy—of immense practical interest to pharmacist and student alike—excellent value at its published price.

THE SHAPE OF THINGS TO COME. By H. G. Wells. The Macmillan Company, New York. $2.50.

If one rereads some of Wells' writings, published in the decade prior to the World War, and compares the events foretold with those which actually followed, Wells' gift as a prophet will be conceded.

In this book Wells covers the political, social, and economic history of mankind from the year 1900 on into the twenty-first century.

John Uri Lloyd's famous book, "Etidorpha," was based upon an imaginary manuscript which fell into the author's hands. Wells imitates Lloyd in that his work follows a dream manuscript, written in the year 2106, which came to him in a mysterious way.

In an historical, logical chronicle, Wells details the things that are to come about during the next two hundred years. Calmly reflecting upon the vivid picture the reader will be inclined to admit that these events might well happen.

After the recovery and boom period following the World War comes the depression years, through which we are now passing. Continental wars 1933-1943 open up a world conflict.

If ordinary everyday war is "hell," these wars were hell, fire and brimstone poured out relentlessly. All the new explosives, invented by man or Satan, were brought into action. Suffocating, deadly gases.

Fire bombs, that started unextinguishable fires, destroyed homes, cities and towns. Devastation, pillage, death and destruction raged. Commerce and living was carried on in concrete subterranean caverns. All people, men, women and children, lived in the war zone. They put on uniforms and wore gas masks around their necks.

This reminds us that as these lines are being written the civilian population of France and other countries are being prepared for war by being drilled in the use of gas masks.

Of interest to pharmacists is the statement that as wars spread the care of the sick and injured was placed under military control. Doctors, nurses, pharmacists donned a black and yellow checkered uniform; hospitals carried the same insignia. Citizens taken sick were at once labeled with a numbered tag, put in a black and yellow uniform, and transported to the government-controlled hospital. A military expansion of the panel system for medical care.

In the continuing wars, the nations of Europe, with England, and including the United States, were involved. One after another of the armies and navies collapsed. Food supplies were exhausted, trade and money disappeared.

In 1949 came a "suspension of hostilities." "Peace of Exhaustion" was arranged. The people of the world had become too weak to fight; they had almost lost their vitality to live; they had no power of resistance against hunger, disease, or death. Warfare had passed into political fiascos—unpayable debts, universal panic, famine and fever.

For more than two years pestilence stalked the earth day and night. The depleted strength of the populations, and the collapse of sanitary services, gave infection full scope. Varieties of influenza, impoverishing fevers, cholera, bubonic plague, with a "maculated fever," became the final victors. The "raid" of germs destroyed more than half of the world's inhabitants.

Incredible as it may seem, the world is now headed toward a similar disaster. Depression has reduced our power of resistance to disease; we are illy fitted to withstand an onrush of epidemics. We have weakened our lines of defense against contagion; we have relaxed our measures of sanitation; we have weakened our health-protecting agencies by cutting their appropriations. Health defense is nearing its weakest point. Soon we can reach a state whereby contagion can sweep the earth.

According to Wells, after the European collapse America went into liquidation, and became disrupted as a nation about 1960. Out of the wreckage there arose the framework of a new world order. Slowly, with many slips and setbacks, there was formed a World State—a new government of the whole world. Under the "Council for World Affairs" there came a control of business activities, educational and hygienic services, production distribution—the general conduct of affairs over the whole earth. There was instituted one human commonwealth.

One may wonder as to what will happen to the drug store in that coming. Well, the apothecary shop, the pharmacy, the drug shop, has held a place for forty centuries. It has survived the fall of empires, nations, and races. It has lived through hundred-year wars, civil wars, world wars. A century, or ten centuries hence, the drug store will be found on, or just around the corner. One will probably recognize it by the still living symbol of the show globe, or the mortar and pestle.

Pharmacy in the past has come forward with, or in, the vanguard of scientific advancement. It will find a place in the new made world. It will be an evolution of the type of thousands that exist here and now. It will be a place of business, or it cannot exist. It will meet and conquer competition in character, not in underhand methods or cut prices. It will aim at the highest standards. It will give a higher, a better, an ever-growing service. It will fill the need of the age in which it may live, and of the humanity which it may serve.

This will be the shape and kind of drug store that is to come.

FRED B. KILMER.

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